Remarks

Claims 1-12 are pending in this application after the entry of new claims 10-12. Claim 1 is amended herein to more distinctly claim the invention. Claims 2-6 and 8 are withdrawn from consideration as being drawn to non-elected inventions. New claims 10-12 are added herein. Support for these amendments and new claims can be found in the original claim language and throughout the specification, as set forth below. It is believed that these amendments and new claims add no new matter. Applicant acknowledges entry of the Declaration under 37 C.F.R. § 1.132, filed March 1, 2002. In light of these amendments, new claims, the Declaration and the following remarks, applicant respectfully requests reconsideration of this application, entry of these amendments and new claims, and allowance of the claims to issue.

35 U.S.C. §102

Claims 1 and 9 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Rosenberg *et al.* (*Science*, Vol. 233, September 1986, pages 1318-1321). Specifically, the Office Action states that Rosenberg *et al.* teaches a method for treating cancer in a subject comprising eliminating suppressor cells in the subject (via the administration of cyclophosphamide), preactivating lymphocytes from the subject *ex vivo*, wherein the lymphocytes of the subject are pre-activated by contacting the lymphocytes *ex vivo* with tumor cells from the subject, and injecting the pre-activated lymphocytes into the subject, thereby treating the cancer.

Claim 1 is amended herein by adding the phrase "proliferating and mature." Support can be found in the specification on page 42, lines 5-15. The addition of this phrase more particularly points out the novel aspect of the claimed invention, *i.e.*, the elimination of both

proliferating and mature (non-proliferating) suppressor cells for adoptive immunotherapy to be effective.

For a prior art reference to anticipate a claimed invention, each and every element of the claimed invention must be disclosed in that single reference. Further, the disclosure in that single reference must be enabling. If one element of the claimed invention is not disclosed in the prior art reference, there is no anticipation. It is settled law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently." *Verdegaal v. Union Oil*, 814 F2d. 628, 2 USPQ2d 1051 (Fed. Cir. 1987).

Rosenberg *et al.* does not teach eliminating both proliferating suppressor cells and their precursors as well as mature (non-proliferating) suppressor cells as a first step in treating cancer with adoptive immunotherapy. The reference only teaches the use of cyclophosphamide to enhance the effect of tumor-infiltrating lymphocytes in the treatment of cancer. In fact, Rosenberg *et al.* teaches that administering tumor-infiltrating lymphocytes in combination with cyclophosphamide is a more effective treatment for cancer than administering a combination of cyclophosphamide and lymphokine-activated killer cells. The reference does not teach, suggest or motivate a person of skill to add an adjunct agent to the cyclophosphamide regimen to eliminate mature (non-proliferating) suppressor cells before administering adoptive immunotherapy to the subject.

It was known in the art that the cytotoxicity of cyclophosphamide was due to its effect on rapidly proliferating cells. For example, Mastrangelo *et al.*, (*Seminars in Oncology*, Vol. 13, No.2, 1986, pages 186-194), cited by the Office, states that cyclophosphamide "appeared to be working by preventing the development of mature suppressor cells, possibly by selective toxicity for a 'presuppressor' cell." See page 191, col. 2, paragraph 1. Also, attached herewith (shown

as Exhibit A) is an abstract by Adatia, AK, entitled "Cytotoxicity of cyclophosphamide in the rat incisor," *Br J Cancer*, 1975 Aug;32(2):208-18. The author states that "[i]t would seem that of the rapidly proliferating epithelial and mesenchymal odontogenic cells in the basal area of the rat incisor, those in the mesenchyme may be most susceptible to the cytotoxicity of cyclophosphamide." Adatia recognized that cyclophosphamide was cytotoxic to rapidly proliferating cells, not mature (non-proliferating) cells.

Applicant was aware of the art, including the teachings of Rosenberg *et al.* See in the specification page 67, last paragraph. Applicant understood that cytotoxic drugs, for example cyclophosphamide, impair only proliferating suppressor cells and spare the highly mature, end-differentiated (non-proliferating) suppressor cells. See in the specification page 42, lines 5-10. Applicant discovered the novel concept that later relapses could be reduced and therapeutic outcomes could be improved if both proliferating suppressor cells and their precursors as well as mature, resting, well-differentiated (non-proliferating) suppressor cells were eliminated, thereby allowing adoptively transferred immune effector cells to better recognize and kill target tumor cells. Thus, applicant teaches eliminating proliferating and mature (non-proliferating) suppressor cells as a first step in treating cancer in a subject, comprising administering to the subject a cytotoxic agent, for example cyclophosphamide, and monoclonal or polyclonal antibodies that recognize the suppressor cells. See in the specification page 42, lines 5-15.

Because the prior art does not teach eliminating both proliferating and mature (non-proliferating) suppressor cells as a first step in the treatment of cancer with adoptive immunotherapy, there is no anticipation; thus, the rejection of amended claim 1 on the basis of lack of novelty is improper. Therefore, applicant respectfully requests withdrawal of this rejection and allowance of amended claim 1 and dependent claim 9.

35 U.S.C. §103

Claims 1, 7 and 9 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rosenberg *et al.* in combination with the teachings of Berd *et al.* (*Cancer Research*, Vol. 47, May 15, 1987, pages 2727-2732). Specifically, the Office Action re-iterates its interpretation of Rosenberg *et al.* as it applies to claims 1 and 9 and states that Berd *et al.* teaches the administration of a monoclonal antibody which specifically recognizes and substantially depletes suppressor cells *in vivo* with modest toxicity. The Office Action goes on to state that by combining cyclophosphamide with the monoclonal antibody of Berd *et al.*, one of ordinary skill in the art would have a reasonable expectation that the combination of the two agents would result in the removal of more suppressor cell activity resulting in increased anti-tumor and or (*sic*) therapeutic response to adoptive immunotherapy.

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *See In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967); *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). "It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *Id.* In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *See In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). In order for a reference to be effective prior art under 35 U.S.C. § 103, it must provide a motivation whereby one of ordinary skill in the art would be led to do that which the appellant has done. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed.

Cir. 1983). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). "When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned." *In re Deuel*, 51 F.3d 1552, 1557, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995) (citing *Fine*, 837 F.2d at 1074).

The Office Action alleges that the suggestion to combine prior art teachings can be found in the cited references. However, the present rejection does not find the required suggestion in either source. Nowhere has it been shown or argued that those of ordinary skill in the art had any general knowledge relevant to eliminating proliferating and mature (non-proliferating) suppressor cells prior to administering adoptive immunotherapy to treat cancer in a subject. Instead, the rejection points to a motivation to achieve the result accomplished by applicant. This is insufficient for at least two reasons. First, any motivation to achieve applicant's result relies on impermissible hindsight. That is, it is all too easy to discover reasons why those in the art would have wanted to achieve an applicant's results after the fact. Second, and more significantly, a motivation to achieve a result is not the same as a motivation to accomplish that goal in a particular way. Motivation to eliminate "more suppressor cell activity resulting in increased anti-tumor and/or therapeutic response to adoptive immunotherapy" (see Office Action, page 5) is not the same as motivation to eliminate both proliferating and mature (non-proliferating) suppressor cells by contacting the suppressor cells with a cytotoxic agent, for example cyclophosphamide, and monoclonal or polyclonal antibodies recognizing the suppressor cells, prior to administering adoptive immunotherapy to treat cancer in a subject. Nothing about the proffered motivation points to applicant's method.

The current rejections are analogous to the rejection deemed improper in *In re Deuel*, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). In this case, the court reaffirmed that a rejection based on an "obvious to try" standard was improper. The court specifically found that prior art that teaches a method for obtaining a general result, when the actual results are unknown, is insufficient to make obvious the actual results obtained upon which the claims are based.

As stated above, Rosenberg *et al.* does not teach, suggest or motivate a person of skill to add any adjunct agent, in particular monoclonal or polyclonal antibodies that recognize suppressor cells, to more completely eliminate suppressor cells. Instead, the reference teaches that cyclophosphamide enhances the effect of tumor-infiltrating lymphocytes in the treatment of cancer.

Berd *et al.* teaches that administering anti-Leu 2a monoclonal antibodies to a human suppressor cytotoxic T-cell subset in patients with advanced cancer decreased the number of circulating Leu 2 (+) lymphocytes. The reference speculates that "it is possible that significant reduction of Leu 2(+) T-cell numbers could lead to augmentation of the response to tumor-associated antigens and tumor regression if the reduced levels could be maintained for weeks or months, instead of days. However, it seems more likely that successful immunotherapy of human cancer will require several immunological manipulations, one of which might be depletion of suppressor T-cells." The reference does not teach, suggest or motivate a person of skill in the art to administer such antibodies as an adjunct agent to enhance the effect of cyclophosphamide in the first step of treating cancer with an expectation of success. In fact, Berd *et al.* does not give any guidance as to what direction therapy should go, and more specifically, the reference does not suggest the need to eliminate both proliferating and mature

(non-proliferating) suppressor cells as the first step in treating cancer with adoptive immunotherapy.

Neither Rosenberg *et al.* nor Berd *et al.*, alone or in combination, suggests the need to eliminate both proliferating and mature (non-proliferating) suppressor cells as the first step in adoptive immunotherapy for treating cancer in a subject. Only with the knowledge of the present invention and impermissible hindsight can a rejection of claims 1, 7 and 9 be made on the basis of obviousness. Thus, the Office Action fails to make a *prima facie* case for obviousness. Applicant, therefore, respectfully requests that these rejections be withdrawn and that amended claim 1 and dependent claims 7 and 9 be allowed.

New claims 10-12

For the reasons stated above, new claims 10-12 are patentable because the prior art does not teach eliminating proliferating and mature suppressor cells in the subject, comprising contacting the suppressor cells with a cytotoxic agent, for example cyclophosphamide, and monoclonal or polyclonal antibodies recognizing the suppressor cells. Therefore, applicants respectfully request allowance of new claims 10-12.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending claims are believed to be warranted, and such action is respectfully requested. The Examiner is invited to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issuance.

Credit Card Payment Form PTO-2038 authorizing payment in the amount of $510.00 (fee for a three (3) month extension of time) is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any deficiency or to credit any overpayment to Deposit Account No. 14-0629.]

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Bruce H. Becker, M.D., J.D. — Date: 1/4/05

1: Br J Cancer. 1975 Aug;32(2):208-18.

Cytotoxicity of cyclophosphamide in the rat incisor.

Adatia AK.

Three of the 4 groups of 3 Wistar rats each were given 40 mg, 80 mg and 12(mg cyclophosphamide/kg respectively by single intraperitoneal injections. Tl fourth group was given 2 ml of normal saline as control. One animal from ea group was killed after 1, 4 and 8 days. The incisor teeth of all experimental animals showed evidence of cytotoxic injury, which appeared to be more sev with increasing dosage, to the undifferentiated mesenchymal cells in the proliferating zone of the pulp close to the basal odontogenic epithelium, cessation of root growth and relative acellularity of the basal area of the pulp Evidence of cytotoxicity to the odontogenic epithelium was seen only in the groups given 80 mg/kg and 120 mg/kg. Resolution of the cytotoxic injury an re-establishment of normal basal odontogenesis were seen in the 40 mg dose group by the eighth day but appeared to be slower with increasing dosage. It would seem that of the rapidly proliferating epithelial and mesenchymal odontogenic cells in the basal area of the rat incisor those in the mesenchyme may be most susceptible to the cytotoxicity of cyclophosphamide. The odontogenic epithelium may be resistant to the cytotoxicity of 40 mg cyclophosphamide/kg. The results may be of significance in the investigatior the mechanism of cytotoxicity of this cancer chemotherapeutic agent.

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